Title:

Heat acclimation improves sweat gland function and lowers sweat sodium concentration in an adult with cystic fibrosis.

Running Title:

Heat acclimation and cystic fibrosis

Authors:

Ashley G.B. Willmott[1,2], Robert Holliss[1], Zoe Saynor[3], Jo Corbett[3], Adam J. Causer[4] and Neil S., Maxwell[1]

Address for Authors:

[1] Environmental Extremes Laboratory, University of Brighton, Eastbourne, UK,

[2] Cambridge Centre for Sport and Exercise Sciences, School of Psychology and Sport Science, Anglia Ruskin University, Cambridge, UK

[3]School of Sport, Health and Exercise Science, University of Portsmouth, Portsmouth, UK

[4] Department for Health, University of Bath, Bath, UK

Details for the Corresponding Author:

Ashley Willmott – Ash.willmott@anglia.ac.uk - Cambridge Centre for Sport and Exercise Sciences, School of Psychology and Sport Science, Anglia Ruskin University, Compass House Annex, East Road, CB5 8DZ, Cambridge, UK

Abstract Word Count: 150 words

Word Count: 1,440 words

Tables: 1

Figures: 0

References: 5

Abbreviations: [Na^+] – sodium concentration; TEM – typical error of measurement; $\dot{V}O_{2max}$ – maximal oxygen uptake; pwCF – people with cystic fibrosis; FEV_1 – forced expiratory volume in 1 second; W_{peak} – peak power output.

Declarations of interest: None

Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT author statement: Neil Maxwell, Zoe Saynor and Jo Corbett: Conceptualisation; Supervision; Writing - review & editing. **Rob Holliss and Adam Causer:** Data curation; Investigation; Project administration; Resources; Writing – review & editing. **Ashley Willmott:** Methodology; Formal analysis; Writing - original draft.

Highlights:

- Heat acclimation improved sudomotor function in an adult with cystic fibrosis (CF)
- Sweat loss increased and sweat [sodium] decreased following heat acclimation.
- Adaptations were maintained for 7-days, with no evidence of heat acclimation decay.
- Heat acclimation was well tolerated and appeared to be safe in an adult with CF.
- Heat acclimation using controlled hyperthermia may benefit people with CF.

ABSTRACT

We present novel data concerning the time-course of adaptations and potential benefits of heat acclimation for people with cystic fibrosis (pwCF), who are at greater risk of exertional heat illness. A 25-year-old male (genotype: delta-F508 and RH117, forced expiratory volume in 1-second: 77% predicted and baseline sweat [Na^+]: 70 mmol·L^{-1}), who had previously experienced muscle cramping during exercise in ambient heat, underwent 10-sessions of heat acclimation (90-min at 40°C and in 40% relative humidity). Adaptations included; lower resting core temperature (-0.40°C) and heart rate (-6 beats·min^{-1}), plasma volume expansion (+6.0%) and, importantly, increased sweat loss (+370 mL) and sweat gland activity (+12 glands·cm^2) with decreased sweat [Na^+] (-18 mmol·L^{-1}). Adaptations were maintained for at least 7-days, with no evidence of cramping during follow-up exercise-heat stress testing. These data suggest pwCF may benefit from heat acclimation to induce sudomotor function improvements, particularly reductions in sweat [Na^+], however, further research is required.

(150 / 150 words)

Key words: Heat acclimation; cystic fibrosis; sweat sodium concentration; adaptation; heat stress

BACKGROUND

Standard care involves encouraging a physically active lifestyle for all people with cystic fibrosis (pwCF). PwCF may be at an increased risk of exertional heat illness during prolonged exercise and/or exercise in higher ambient temperatures [1]. Specifically, as mutant CF transmembrane conductance regulator proteins reduce ion reabsorption capacity within the sweat duct, pwCF produce sweat with higher sodium ([Na^+]) and chloride ([Cl^-]) concentrations [2]. As such, pwCF are more susceptible to electrolyte imbalances, hyponatremia and dehydration (via inadequate fluid ingestion, reduced osmotic drive for thirst and an absence/suppressed thirst sensation), which may all predispose exertional heat illness [3]. However, currently there is limited understanding regarding strategies that may help mitigate these risks.

One potential strategy is through physiological adaptive mechanisms (e.g. increased sweat rate and diluted sweat electrolyte concentrations), as observed in healthy individuals following repeated bouts of exercise-heat stress (i.e. heat acclimation) [4]. However, little is known concerning the effectiveness of this strategy, and the time-course and maintenance of adaptations in pwCF. Orenstein et al. [1] reported similar thermoregulatory (lower rectal temperature) and cardiovascular adaptations (lower heart rate) in pwCF versus healthy controls, following 8-days of heat acclimation. However, sudomotor function remained unchanged in pwCF, whereas healthy individuals displayed reductions in sweat [Na^+] and [Cl^-], suggesting an inability to adapt, a disparity in the time-course of adaptations and/or a sub-optimal heat acclimation protocol [1].

Therefore, this case study aimed to investigate how a young man with moderate CF lung disease and a history of muscle cramping during exercise in heat stress, adapted to 10-sessions of heat acclimation, with a particular emphasis on the time-course and maintenance of heat adaptations, specifically, sweat gland function and sweat [Na^+].

METHODS

A recreationally active 25-year-old-male (height: 169.9 cm, body mass: 77.8 kg, body fat: 19.8%) gave informed consent to participate in this study, which was approved by our Institutional Ethics Committee and complied with the principles of the Declaration of Helsinki (2013). He had moderate CF lung disease as indicated by his genotype (delta-F508 and R117H), forced expiratory volume in 1 second (FEV_1: 77% predicted) and baseline sweat [Na^+] (70 $mmol{\cdot}L^{-1}$). He played football thrice weekly and ran regularly but previously had reported signs and symptoms of heat-related illnesses (heat cramps and heat exhaustion) during prolonged exercise in temperate/hot environmental conditions (London and Brighton marathons).

The participant completed a maximal cardiopulmonary exercise test [5] at 22°C and in 40% relative humidity to determine aerobic fitness (maximal oxygen uptake [$\dot{V}O_{2max}$]: 3.50 $L{\cdot}min^{-1}$ and 45.0 $mL{\cdot}kg^{-}$

$^{1}\cdot min^{-1}$ [117.4% predicted]), peak power output (W_{peak}: 261 W and 3.4 $W\cdot kg^{-1}$ [119.7% predicted]) and to prescribe exercise intensities for his heat acclimation state test (3, 4.5 and 6 $W\cdot kg^{-1}$) [4]. Heat acclimation state tests were completed at 45°C and in 20% relative humidity; 2-days pre- (PRE), midway through- (MID), 2-days post- (POST) and 7-days post-heat acclimation (POST+7-days). Heat acclimation included ten 90-min exercise sessions of controlled hyperthermia. This involved cycling at 65% $\dot{V}O_{2max}$ (2.2 $W\cdot kg^{-1}$) to achieve a target rectal temperature of 38.5°C, then using variable exercise intensities to maintain this target temperature for the remainder of the session. Heat acclimation occurred at 40°C and in 40% relative humidity, over two consecutive 5-day periods (i.e. 5-days heat acclimation, rest day, heat acclimation state test, rest day, 5-days heat acclimation).

Physiological (rectal and skin temperature, heart rate, plasma volume, whole-body sweat loss and rate, local sweat rate, sweat gland activity and sweat [Na^+]) and perceptual measures (using fixed-point categorical scales for: rating of perceived exertion [from 6 "*No exertion*" to 20 "*Maximal Exertion*"], thermal sensation [from 0 "*Very Very Cold*" to 4 "*Neutral*" to 8 "*Very Very Hot*"] and thermal comfort [from 0 "*Very Comfortable*" to 5 "*Very Uncomfortable*") were assessed during each visit, as described previously [4]. Briefly, whole-body sweat loss was estimated from nude body mass differences pre- to post-exercise (Adam Equipment Inc., USA), local sweat rate was estimated from technical absorbent patches (Tegaderm+Pad, 3M™, USA) on the upper back, sweat gland activity was estimated using the modified iodine technique, and sweat [Na^+] measured using a Sweat-Chek™ analyser (Wescor Inc., USA). Predefined analytical limits and typical error of measurements (TEM) were used to highlight meaningful adaptations following heat acclimation [4].

RESULTS

Heat acclimation intervention:

The participant completed all of the scheduled sessions with no adverse incident, cramping or other heat-related illness reported. The thermal forcing-function was maintained throughout, as indicated by the consistent attainment of the target rectal temperature (Table 1).

MID-heat acclimation state test:

After 5 exercise-heat sessions thermo-physiological adaptations were evident, including reduced resting rectal temperature (-0.21°C; 53% of final adaptation), resting heart rate (-8 beats.min^{-1}; 133% of final adaptation) and peak heart rate (-19 beats.min^{-1}; 173% of final adaptation) (Table 1). Sudomotor adaptations were also evident, including reduced sweat [Na^+] (-11 mmol·L^{-1}; 61% of final adaptation), and increased sweat gland activity (+12 glands·cm^2; 100% of final adaptation) and local sweat rate at the back (+0.36 mg·min^{-1}·cm^2; 78% of final adaptation). The participant perceived the MID-heat acclimation state test to be easier (peak rating of perceived exertion -2 [arbitrary units]) and felt cooler (peak thermal sensation -1 [arbitrary units])

POST-heat acclimation state test:

Further reductions in resting rectal temperature (-0.19°C vs. MID; -0.40°C vs. PRE) and sweat sodium [Na^+] (-7 mmol·L^{-1} vs. MID; -18 mmol·L^{-1} vs. PRE) were evident. Peak rectal temperature was reduced relative to the MID-heat acclimation state test (-0.24°C), and a reduction in skin temperature (rest -0.96°C, peak -0.43°C), expansion of plasma volume (+6.0%) and increased whole-body sweat loss (+370 mL) were also evident relative to PRE-heat acclimation state test (Table 1).

POST+7-days heat acclimation state test:

The majority of adaptations, including sudomotor enhancements (whole-body sweat loss, sweat [Na^+] and sweat gland activity), were maintained for 7-days after heat acclimation (Table 1). A strong negative correlation (r = 0.95) was observed between sweat [Na^+] and whole-body sweat loss during the course of heat acclimation (Table 1).

DISCUSSION

We observed changes in classic markers of heat adaptation following 5 and 10-sessions of heat acclimation in an adult with moderate CF lung disease, consistent with typical responses in healthy adults of a similar age [4]. Our data demonstrated a rapid time-course of adaptation in several parameters (including; heart rate, sweat gland activity, local sweat rate at the back), with ~ 75% of the final adaptation achieved after only 5-sessions; yet, other parameters required longer to evoke a substantial change. After 10-sessions of heat acclimation, we observed lower resting rectal temperature and heart rate; plasma volume expansion; increased whole-body sweat loss, sweat gland activity and local sweat rate; and reduced sweat $[Na^+]$.

A seminal study by Orenstein and colleagues in 1984 investigated whether pwCF could heat-acclimate using an 8-day exercise heat acclimation protocol (70-min exercise at 50% $\dot{V}O_{2max}$; ~37-38°C, 33-55% relative humidity). PwCF demonstrated some thermo-physiological adaptations, including a reduced resting rectal temperature (-0.2°C), lower peak exercise rectal temperature (-0.4°C) and heart rate (-15 $b \cdot min^{-1}$). However, it was concluded that heat acclimation did not alter sweat gland function or sweat electrolyte concentration in pwCF. Our data contrasts with Orenstein et al. [1], demonstrating for the first time, a range of important sudomotor adaptations following heat acclimation. The increased sweat loss (1.93 to 2.30 L) and reduced sweat $[Na^+]$ (70 to 52 $mmol \cdot L^{-1}$) observed in the participant with moderate CF involvement are consistent with the sudomotor responses of healthy individuals following a similar heat acclimation protocol (+533 mL and -27 $mmol \cdot L^{-1}$ [4]). These adaptations are likely to reduce the risk of predisposing factors to exertional heat illness (e.g. electrolyte imbalance, cramping, and hyponatremia) and suggest that this individual improved his heat tolerance without reporting further cramping issues. However, further investigations are warranted to understand why this strategy has not been widely utilised by pwCF, particularly athletes, most likely due to a lack of research-informed practice and logistical challenges, with the potential for other, more time-efficient approaches (e.g. saunas/hot baths and/or pre-cooling) also requiring investigation in this population.

Another unique observation is that the adaptations were maintained for at least 7-days after heat acclimation (Table 1). This is an under-investigated area in pwCF and our data provides practical information for those interested in heat acclimation to minimise performance and/or health impairments anticipated during athletic events. Future studies should investigate the effect of heat acclimation on sweat [Cl^-] in pwCF (a limitation of this case report), given this prognostically-relevant outcome is known to decrease following heat acclimation in healthy individuals.

CONCLUSION

This case report demonstrates how heat acclimation may benefit pwCF and potentially lower the risk of exertional heat illness, which is particularly important for pwCF exercising in hot climates. Future studies to confirm these findings in a larger representative sample are needed to further understand the benefits from heat acclimation for pwCF.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the participant in this case study for his dedication during testing.

(1,440 / 1,200 words)

REFERENCES

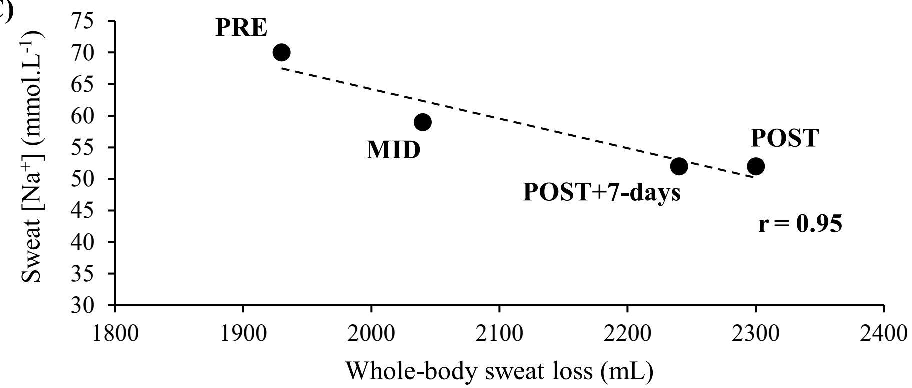
1. Orenstein, D. M., Henke, K. G., & Green, C. G. (1984). Heat acclimation in cystic fibrosis. *Journal of Applied Physiology*, *57*(2), 408-412.
2. Williams, C. A., Saynor, Z. L., Tomlinson, O. W., & Barker, A. R. (2014). Cystic fibrosis and physiological responses to exercise. *Expert review of respiratory medicine*, 8(6), 751-762.
3. Pryor, J. L., Périard, J. D., & Pryor, R. R. (2020). Predisposing Factors for Exertional Heat Illness. In Exertional Heat Illness (pp. 29-57). Springer, Cham.

4. Willmott, A. G., Hayes, M., James, C. A., Dekerle, J., Gibson, O. R., & Maxwell, N. S. (2018). Once-and twice-daily heat acclimation confer similar heat adaptations, inflammatory responses and exercise tolerance improvements. *Physiological reports*, *6*(24), e13936.
5. Causer AJ, Shute JK, Cummings MH, Shepherd AI, Bright V, Connett G, et al. Cardiopulmonary exercise testing with supramaximal verification produces a safe and valid assessment of $\dot{V}O_{2max}$ in people with cystic fibrosis: a retrospective analysis. *Journal of Applied Physiology* 2018;125:1277–83.

Table 1. Mean ± SD data for: (A) heat acclimation sessions; (B) differences in heat adaptations as evaluated by repeated heat acclimation state tests; and (C); correlation between sweat [Na+] and whole-body sweat loss.

(A) Heat acclimation	Session 1	1 to 5	6 to 10	1 to 10
Time to 38.5°C (min)	60	59 ± 9	57 ± 6	58 ± 7
Peak rectal temperature (°C)	38.62	38.62 ± 0.12	38.65 ± 0.06	38.63 ± 0.09
Change in rectal temperature (°C)	1.49	1.51 ± 0.14	1.61 ± 0.06	1.56 ± 0.12
Mean heart rate ($b \cdot min^{-1}$)	159	151 ± 8	143 ± 3	147 ± 7
Peak heart rate ($b \cdot min^{-1}$)	176	175 ± 5	174 ± 3	174 ± 4
Whole-body sweat loss (mL)	1830	1892 ± 167	2156 ± 132	2024 ± 199
Whole-body sweat rate($L \cdot hr^{-1}$)	1.22	1.26 ± 0.11	1.44 ± 0.09	1.35 ± 0.13
Peak rating of perceived exertion	19	19 ± 1	18 ± 0	18 ± 1
Peak thermal sensation	7	8 ± 0	7 ± 0	8 ± 0
Peak thermal comfort	4	5 ± 0	5 ± 0	5 ± 0

(C)



(B) Heat acclimation state tests	PRE	PRE to MID	MID to POST	PRE to POST	PRE to POST+7-days	POST to POST+7-days	Criteria (±)	Adapted 1 to 5	Adapted 6 to 10	Adapted 1 to 10	Maintained
Rest rectal temperature (°C)	37.25	-0.21	-0.19	-0.40	-0.36	+0.04	0.20	✓	✗	✓	✓
Peak rectal temperature (°C)	38.30	+0.10	-0.24	-0.14	-0.16	-0.02	0.20	✗	✓	✗	✓
Rest skin temperature (°C)	31.86	+0.94	-1.90	-0.96	-1.40	-0.45	0.24	✗	✓	✓	✓
Peak skin temperature (°C)	37.53	+0.92	-1.35	-0.43	-0.21	+0.21	0.24	✗	✓	✓	✓
Rest heart rate ($b \cdot min^{-1}$)	71	-8	+2	-6	-16	-10	5	✓	✗	✓	✓
Peak heart rate ($b \cdot min^{-1}$)	191	-19	+8	-11	-26	-15	5	✓	✓	✓	✓
Plasma volume (%)	-	+0.7	+5.3	+6.0	+4.4	-1.6	5	✗	✓	✓	✓
Sweat setpoint (°C)	37.67	-0.13	-0.05	-0.18	-0.04	+0.14	0.21	✗	✗	✗	✓
Sweat gain ($g \cdot sec^{-1} \cdot °C^{-1}$)	0.50	-0.09	+0.08	-0.01	+0.01	+0.02	0.09	✗	✗	✗	✓
Whole-body sweat loss (mL)	1930	+110	+260	+370	+310	-60	200	✗	✓	✓	✓
Sweat [Na^+] ($mmol \cdot L^{-1}$)	70	-11	-7	-18	-18	0	2	✓	✓	✓	✓
Sweat gland activity ($gland \cdot cm^2$)	113	+12	0	+12	+16	+4	5	✓	✗	✓	✓
Local sweat rate ($mg \cdot min^{-1} \cdot cm^2$)	0.52	+0.36	+0.10	+0.46	+0.44	-0.02	0.13	✓	✗	✓	✓
Peak rating of perceived exertion	20	-2	+1	-1	-3	-2	1	✓	✗	✓	✓
Peak thermal sensation	8	-1	0	-1	-2	-1	1	✓	✗	✓	✓
Peak thermal comfort	5	0	0	0	-1	-1	1	✗	✗	✗	✓

Note: ✓ - yes; ✗ - no.